V.—WITH SODIUM HYPOBROMITE.
Found: 47.22; 47.83; 47.66

Investigations on similar lines are being continued.

CALCUTTA, INDIA.

[FROM THE RESEARCH LABORATORY OF PARKE, DAVIS & COMPANY.]

STUDIES ON DERIVATIVES OF TRIHALOGENTERTIARY-BUTYL-ALCOHOLS.

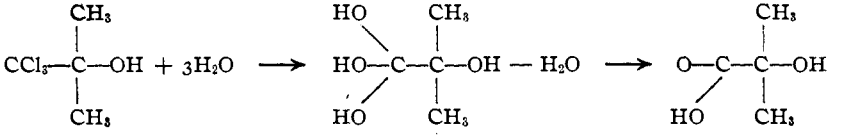
I. THE ACETIC ESTER OF TRIBROMOTERTIARY-BUTYL-ALCOHOL OR BROMETONE ACETIC ESTER.

BY T. B. ALDRICH AND C. P. BECKWITH.

Received September 27, 1916.

The trichloro- and tribromotertiary-butyl-alcohols are most interesting compounds, both chemically and pharmacologically. The trichloro-compound, "Chloretone,"[1] has pronounced hypnotic, sedative and anesthetic properties, both local and general, and the same may be said of the tribromo-compound, "Brometone,"[2] which is considered to have more marked sedative, but less pronounced hypnotic and anesthetic properties. Both compounds are sparingly soluble in water (chloretone 0.8% and brometone still less), but readily soluble in the organic solvents; both have a camphor-like odor and taste, are readily volatile in the air or with steam, and may be crystallized from dilute alcohol and obtained in the form of beautiful white crystals. Both compounds combine with water more or less firmly and in this respect resemble chloral, although the water is not chemically bound as in the latter substance to form a stable hydrate.

The three halogens attached to one carbon atom impart to these bodies properties different from those of the unsubstituted tertiary alcohols; indeed, as pointed out by Willgerodt,[3] they may be regarded as trihalides of *o*-α-hydroxyisobutyric acid, for they yield α-hydroxyisobutyric acid upon treatment with alkalies under suitable conditions, probably thus:



The trichlorotertiary-butyl-alcohol may be crystallized from warm moderately concentrated nitric acid without material decomposition. With care the tribromo-alcohol may be similarly crystallized, though with considerable decomposition. They are broken down by concentrated sulfuric acid and by moderately dilute caustic alkali solutions(5%). In general, they are chemically rather inert bodies, fairly resistant to anything

[1] Chloretone and [2]brometone are the commercial names given the trichloro- and tribromotertiary-butyl-alcohols, respectively.

[3] *Ber.*, 15, 2305 (1882).

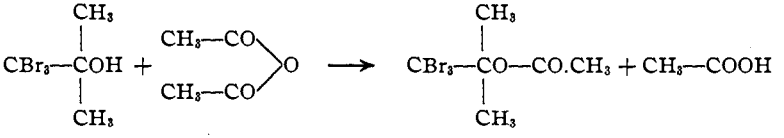
short of destructive treatment. Willgerodt was unable to replace the chlorine of chloretone by alkyls.[1] It is interesting to note, however, that they form readily a series of esters of remarkable properties, and it is principally with these esters and related compounds that we are concerned in these articles.

It may be well to say in anticipation that one of the most striking properties of this series of esters is their relatively great stability—a fact that was noted by one of us (C. P. B.) in 1903. At that time the salicyclic ester of trichlorotertiary-butyl-alcohol was prepared and studied chemically and pharmacologically in the hope that it might be found to possess therapeutic value comparable with that of salol. The substance proved to be quite resistant to more or less heroic chemical treatment and to pass through the alimentary tract unchanged. Pharmacologically and clinically it appeared to be almost, if not quite, inert. These findings were not published at the time and later the compound was produced in Germany and patented.[2]

An observation very useful in the purification of these esters is that all of them, so far prepared by us, seem to be quite unaffected by gentle warming with caustic alkali solutions of 5–10%, while the uncombined alcohols themselves are broken down and readily removed by this treatment.

In a former article one of us[3] obtained by acetylating trichlorotertiary-butyl-alcohol with acetic anhydride and anhydrous sodium acetate in the usual manner, an ester to which the name acetyl chloretone was given. It has since been noted that this ester had already been prepared and briefly described by Willgerodt[4] under the unusual name, however, of acetyl-oxy-isobutyric-acid-trichloride.

The present article is concerned chiefly with the preparation and properties of a like compound of tribromortertiary-butyl-alcohol, the brometone acetic ester being formed similarly to the chloretone ester according to the following equation:



Preparation.—(*a*) One part of brometone is boiled with two parts of acetic anhydride and one part of anhydrous sodium acetate for two hours, using a reflux condenser. During the heating, the mixture becomes slightly colored, due, no doubt, to the splitting off of bromine or bromine

[1] *J. prakt. Chem.*, **39**, 283–289 (1889).
[2] R. Wolffenstein, D. R. P. No. 267,381.
[3] T. B. A., THIS JOURNAL, **37**, 2720 (1915).
[4] *J. prakt. Chem.*, **39**, 283–289 (1889).

compounds. On cooling, the mixture solidifies and on adding water and allowing to stand for some time two layers form, the upper being water, acid, sodium acetate, etc., the lower containing the product desired.

The upper layer is decanted as closely as possible, the residue warmed gently with an excess of caustic soda solution, and after standing some time extracted with ether. The ethereal extract is washed thoroughly, then filtered and the ether allowed to evaporate. The residue left is distilled with steam. A colorless oil passes over, having an odor very similar to, but not so pronounced as that of chloretone acetic ester. It is collected with ether, filtered, and the ether allowed to evaporate. Yield of nearly 50%. It colored slightly yellow on standing, and solidified. When purified by recrystallizing from alcohol it is white and melts at 43–44° (uncorr.).

(*b*) The following method of preparation is simpler and gives nearly a quantitative yield:

Dissolve two parts of brometone in four parts of glacial acetic acid and to this solution add one and a half parts of acetyl bromide or one part of the chloride. The mixture becomes warm and fumes of the halogen acid are given off. After the reaction has proceeded at room temperature for some time, the flask is heated on the steam bath for two hours and then allowed to stand overnight. Dilute caustic alkali is then added and the mixture warmed to decompose any excess of acetyl haloid or brometone. The ester settles then to the bottom of the vessel as an oil. The water etc., above the oil is decanted and the latter washed several times with water. This oil on cooling strongly, and especially when inoculated with a crystal of the ester, solidifies at once in crystalline form. It may be recrystallized from alcohol. The yield is nearly quantitative.

The preparation may also be carried out without the use of glacial acetic acid as a diluent. In this case the acetyl haloid is poured directly on the brometone, but considerable heat is evolved and it is advisable to provide for adequate cooling. After the reaction is ended, the vessel is heated on the steam bath until very little acid is given off. The compound is then treated as in the other cases.

Whichever method is used, economy of acetylating reagents is served, no doubt, by preliminary drying of the brometone as far as practicable. On the other hand, attempts to dry brometone thoroughly by most of the usual methods entail loss of this substance through volatilization, decomposition, or otherwise. For use in the reaction under discussion, a few days' standing in a desiccator over calcium chloride will suffice. (Sulfuric acid should not be used as a drying agent, since it absorbs and decomposes brometone vapor.) In fact, save that a larger proportion of the acetylating reagent is required, there is no objection to using ordinary crystallized brometone without preliminary drying.

Bromine determinations (Carius) carried out with a product recrystallized several times from moderately strong alcohol and melting at 43–44°, gave the following results:

0.4672, 0.2869, 0.2697, and 0.2584 g. gave 0.3161, 0.1985, 0.1841, and 0.1775 g. Br. Calc. for $C_6H_9O_2Br_3$: 67.99% Br. Found: 67.66, 69.20, 68.26, and 68.69%.

Leaving out the second value the results are sufficiently near, especially when the method of preparation is considered, to characterize the compound, without the necessity of making a combustion analysis, as the brometone acetic ester.

Properties.—The compound is extremely soluble in strong alcohol, acetone, chloroform, ether, glacial acetic acid, benzene, etc., insoluble in water. The alcoholic solution is precipitated by water.

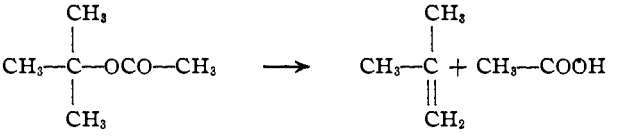
When boiled with water for some time (29 hrs.), using a reflux condenser, a portion of the substance in the form of an oil, estimated at 0.5 of that taken originally, is found undecomposed. This oil on cooling has a tendency to crystallize. The supernatant liquid is strongly acid toward litmus and gives a heavy yellowish precipitate with $AgNO_3$, soluble, though not quickly in an excess of strong ammonia. There is no evidence of the alcohol in the condenser, as was the case when the chloretone ester was treated similarly. No brometone or other body is thrown out by diluting the supernatant liquid with water. Further boiling for 21 hours completely decomposes the remainder of the oil. Probably the brometone ester is saponified and then the brometone decomposed. When brometone acetic ester is boiled with water, to which H_2SO_4 has been added, decomposition takes place in about the same time as when water alone is used.

Three grams of the substance were placed in a pressure tube with 10 cc. of H_2O and heated for three hours at 160°. There was a slight pressure on opening the tube, a combustible gas was given off, and an oil insoluble in H_2O had formed which did not solidify on cooling in ice water. On reheating the resealed tube for several hours at 170° complete decomposition of the oil-like substance had taken place, the homogeneous liquid had become yellowish, had a strong acid reaction toward litmus and showed the presence of large quantities of hydrobromic acid and of traces of acetic acid. By diluting with water, brometone was not thrown out. Partial carbonization had occurred.

Although saponification takes place slowly by boiling with water or water and dilute sulfuric acid, it takes place very rapidly when the ester is heated with an excess (three or four times its volume) of concentrated nitric acid. In fact, the brometone ester conducts itself in general toward hot nitric acid the same as the chloretone ester, except that the brometone which is produced at first readily undergoes further decomposition if heat is applied too long. In saponifying the brometone ester the procedure is as follows: Heat with the acid over a free flame until the ester

dissolves. Then cool under running water. If a cloudiness appears, the saponification is not far enough advanced. Heat gently until on cooling the solution remains clear, then dilute with an excess of water. The brometone is precipitated amd may be recrystallized from dilute alcohol.

Here again, as with chloretone acetic ester, it is to be noted that saponification may occur with reproduction of the original acid and alcohol, while the usual rule with tertiary alcohols is that an unsaturated hydrocarbon appears instead of the alcohol, thus:



Brometone acetic ester volatilizes slowly, much more slowly than brometone. Placed on a watch glass under a funnel at summer temperature for 12 days, it lost 23% of its weight. In the incubator for 7 days a sample lost 12.5%. Under like conditions the loss of brometone is much greater.

The following preliminary data relative to the pharmacological action of brometone acetic ester as compared with chloretone were kindly furnished by our associate, Mr. L. W. Rowe:

"The toxicity of this preparation was determined by intraperitoneal injection into guinea pigs of an olive oil solution and the minimum fatal dose was found to be 0.5 g. per kg. body weight, that of chloretone being 0.15 g. per kg. body weight.

Because of the practically complete insolubility of the product in water, it was impossible to determine the irritation, if any, which was produced by hypodermic injection. When an olive oil solution was used, some irritation was produced after some hours due to the very slow absorption. When a strongly alcoholic solution was used, irritation was produced immediately by the alcohol. The product itself probably does not possess very irritating properties.

Concerning the anesthetic and sedative action of this drug we can say that as the dose approaches very near the toxic dose, an anesthetic action is observed several hours after administration. The slow action is no doubt due to the very slow absorption of the drug. The anesthetic action, which may be partially due to the toxicity of the drug, is certainly not as strong or as rapidly evidenced as that produced by chloretone.

The action of brometone acetic ester upon the laid-bare frog's heart is not as strong as is that of chloretone.

The blood pressure of an anesthetized dog was somewhat lowered after the intravenous injection of rather large amounts of this drug (4 cc. of a 2% solution in 50% alcohol). A control injection of the same amount of alcohol alone failed to produce as marked a reaction.

In summarizing these data it seems that brometone acetic ester is somewhat similar to chloretone in its pharmacological action but that the action of the former is not nearly as strong or as quickly evidenced. The latter fact can partially be accounted for by the extreme insolubility in water of the brometone acetic ester."

Further pharmacological studies are being made with these esters in comparison with chloretone and brometone.

Owing to delay and confusion in the mails from Germany, there has just reached us an article by R. Wolffenstein, A. Loewy and M. Bachstez on "Esters of Trichlorotertiary-butyl-alcohol and Their Pharmacology."[1] The details of their pharmacological findings are published in a separate article in a number of Schmiedeberg's Archiv. that has not yet come to hand. For the present, it will suffice to say that the results obtained by these gentlemen with the chloretone esters are, in most points, quite in accord with ours with the brometone esters in so far as we have followed parallel lines.

According to these authors the preparation of the esters is ordinarily easily carried out through the action of the acid chloride with or without the aid of tertiary bases, in fact from the acid and the alcohol in the presence of a condensing agent.

The following facts were observed by Wolffenstein relative to the esters of trichlorotertiary-butyl-alcohol: They are not as a rule split up in the body; they exhibit an unexpected action quite different from that of the alcohol from which they are prepared; and they exhibit poisonous properties, causing cramps. These cramps or convulsions begin to manifest themselves in chloretone acetic ester, increasing in the higher homologues and reaching the maximum as far as investigated in the ester of isovaleric acid.

It is further stated that the chloretone acetic ester, the one most thoroughly studied, shows less narcotic action but greater poisonous properties than chloretone.[2] The decrease in narcotic property and increase in poisonous property is shown much more plainly in the propionic ester and still more in the isovaleric ester. The isovaleric ester has no hypnotic action, but has, at least on rabbits, a toxic action causing convulsions.

The authors furthermore state that the only[3] known ester of trichlorotertiary-butyl-alcohol, up until the appearance of their article, is the

[1] *Ber.*, **48**, 2035–43 (1916).

[2] According to the results of Aldrich relative to the toxicity of acetyl-chloretone (trichlorotertiary-butyl acetic ester) it was found (THIS JOURNAL, **37**, 2722 (1915)) that "The toxicity of this acetyl-ester, when introduced subcutaneously into guinea pigs, is slightly less than that of Chloretone." Possibly Wolffenstein and his collaborators employed another method of administration, which would account for the different findings.

[3] Willgerodt prepared also the benzoic ester, *J. prakt. Chem.*, *loc. cit.*

acetic acid ester prepared first by Willgerodt under the name acetyl-oxy-isobuttersäure-trichloride. [Later by Aldrich under the name monoacetyl trichlorotertiary-butyl-alcohol (chloretone acetic ester).]

The following esters of chloretone were prepared by Wolffenstein: Propionic ester (yellow oil); isovaleric ester (oil); bromoisovaleric ester (oil); monochloroacetic ester (cryst.); trichloroacetic ester (cryst.); diethyl glycine ester (oil); dimethyl glycine ester (oil); piperidine acetyl ester (cryst.); allophanic ester (cryst.); acid malonic ester (cryst.); dibromocinnamic ester (cryst.); neutral malonic ester (cryst.).

Summary.

The acetic ester of tribromotertiary-butyl-alcohol is most conveniently prepared through the interaction of acetyl chloride or bromide and the alcohol, or by means of acetic anhydride and anhydrous sodium acetate, in the usual way.

Prepared by either of these processes and recrystallized from alcohol, the purified substance melts at 43–44° (uncorr.).

Bromine determinations (Carius) gave results sufficiently near to characterize the compound as brometone acetic ester with the formula

$$C_6H_9O_2Br_3 = CBr_3—C(CH_3)_2.O.OC—CH_3.$$

The compound is extremely soluble in the organic solvents, practically insoluble in water. It is not readily saponified by boiling with water or acidulated water and when saponified the alcohol is decomposed still further. Although saponification takes place slowly by boiling with water or water and acid, it takes place very quickly when heated with an excess of moderately concentrated nitric acid. Like chloretone and brometone, though not quite so readily, the ester is volatile in the air and especially with steam. The pharmacological action is similar to that of chloretone and brometone although, presumably on account of its greater insolubility in water, its effects are less rapid and marked.

DETROIT, MICH.

[CONTRIBUTION FROM CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY.]

STUDIES IN ESTERIFICATION. VII.

THE ESTERIFICATION OF *o*-, *m*- AND *p*-TOLUIC ACIDS BY ETHYL MERCAPTAN.

BY J. H. SACHS AND E. EMMET REID.

Received September 27, 1916.

Historical.

As early as 1862 Berthelot and Pean de St. Gilles[1] began the investigation of the general problem of esterification. They studied the limit of

[1] *Ann. chim. phys.*, [3] **65**, 385 (1862); **66**, 5 (1862); **68**, 225 (1863).